REMARKS

Claims 2-9, not 1-9 as stated in the final Office Action and subsequent Advisory Actions, are pending in the application. Upon entry of the amendments herein, claims 2-9 remain pending in the application; claim 2 has been amended.

Following issuance of the final Office Action and prior to Applicants' response, the Examiner and Applicants' agent engaged in a substantial telephone discussion, on April 17, 2002. In light of that discussion, it was the understanding of Applicants' agent that the amendments to claim 2 after final rejection, originally submitted as part of Applicants' May 2, 2002 response, and which response was resubmitted directly to the Examiner on July 9, would lead to withdrawal of the indefiniteness rejections of the claim. This was the case because the Examiner and Applicants' agent had discussed specific remedies for the situation, the Examiner had acknowledged that disclosure in support of the remedial language could be found in the specification, specifically on page 6, lines 16-24, and Applicants had employed said disclosure as required in amending the claim.

However, instead, the Examiner issued an Advisory Action, the basis for which was the assertion that the amendments to claim 2 introduced limitations requiring further consideration and search. Subsequent to the issuance of the Advisory Action,

the Examiner and Applicants' agent conducted a further telephone interview, spanning August 27 and 28, 2002. During the interview, the Examiner indicated to Applicants' agent that she would discuss matters with her Supervisor and get back to Applicants' agent prior to any further formal action. However, instead, the Examiner issued a Supplemental Advisory Action providing further explanation of the issues alleged to have been raised by Applicants' amendments.

There should be no argument that the amendments made by Applicants in the wake of the April 17, 2002 telephone discussion between the Examiner and Applicants' agent fill in the alleged gaps in the steps of the claim and more clearly recite the basis for the claimed assay. Again, the Examiner herself had agreed that support for the required amendments existed in the specification and had agreed on the location of said support; Applicants used this disclosure in making their amendments. However, the Examiner has, inappropriately, seized on the amendments as a basis for maintaining the final rejection on grounds of new issues being raised and lack of clarity in the introduced amendments.

It should be noted that, as indicated in the July 22, 2002 Advisory Action and later Supplemental Action, the amendments submitted by Applicants in response to the final Office Action and in the wake of the April telephone discussion with the

Examiner were not entered. Accordingly, the amendments herein are reflective of changes made to claim 2 in the form it existed following Applicants' August 13, 2001 Amendment and Response.

In the July 22, 2002 Advisory Action, the Examiner indicated that new issues were raised by Applicants' introduction of the phrase "to terminate peptidoglycan synthesis" into step (2) of claim 2. As subsequently explained to the Examiner on the telephone, this was certainly an inappropriate basis for maintaining the final rejection. Applicants had gone out of their way to clarify the assay procedure and had added the language in question even though it was not necessary; one of skill in the art would certainly know that the reason for adding chelator in step (2) was to terminate synthesis, whether or not such language was actually to be found in the claim. Furthermore, the connection between termination of synthesis and addition of chelator is disclosed in the instant specification on page 6, lines 9-14. In any event, this language has again been added to claim 2.

In the same Advisory Action, the Examiner also asserted that Applicants' introduction of language reciting the binding of lectin-coated beads to synthesized radiolabelled peptidoglycan also raised a new issue requiring further consideration and search. As the Examiner was reminded during the August telephone interview, the introduced language finds

basis in the instant specification on page 6, lines 16-24; again, the Examiner had previously acknowledged that said passage provided the support required to fill in the alleged gaps in claim 2. This language has been reintroduced, with embellishment, in the amendments herein.

In the Supplemental Advisory Action, the Examiner commented further on the issues allegedly raised by Applicants' amendment of step (3) of claim 2 and set forth a further issue alleged to have been raised in step (4) of the claim.

In the first place, the Examiner further clarified that the "issue" with respect to the binding of beads to peptidoglycan had to do with which element of the beads actually binds. Again, as the Examiner was reminded on the telephone, the language in question was taken from the very passage sanctioned by the Examiner, and any further clarification allegedly required can be found in the same passage. Nonetheless, in the interest of expediting prosecution, Applicants have reintroduced the language called into question by the Examiner, but embellished to recite that the binding is via the lectin component of the beads.

Secondly the Examiner explained that the recitation of "radiolabelled peptidoglycan" in step (3) "lacks clear antecedent support in step 1)." To begin with, it is well known in patent prosecution that antecedent basis per se is not

necessarily required, particularly if common sense would make it apparent to anyone viewing the claim(s) what the connection in question is. Again, Applicants do not understand how this could be considered an appropriate basis for rejection. It would be obvious to anyone of skill in the art that the radiolabelled peptidoglycan of step (3) must be derived from the radiolabelled UDP-*N*-acetyl glucosamine precursor, since the latter is the only radiolabelled component of the reaction mixture of step (1). Such would be obvious even if step (1) did not specifically recite that the reaction mixture is incubated "under conditions suitable for peptidoglycan synthesis." Again in the interest of expediting prosecution, the language called into question by the Examiner has been reintroduced but it has been embellished by the addition of language reciting the radiolabelled precursor.

With respect to step (4), the Examiner asserts that the language introduced by Applicants is ambiguous because no distinction is made between light energy that might be emitted by free beads and light energy emitted by those beads bound to radiolabelled peptidoglycan; in making this assertion, the Examiner raised the question whether or not autofluorescence is possible.

To clarify, then, Applicants wish to advise the Examiner that the fluorescer must be activated by some outside stimulus, in the present context radiation energy, to emit light; thus,

there would be no autofluorescence. One of skill in the art would be aware of these facts. Nonetheless, again in the interest of expediting prosecution, Applicants have reintroduced the language called into question by the Examiner but embellished with the recitation that the light energy emitted by the fluorescer is triggered by the bound, radiolabelled peptidoglycan, which is in proximity to said fluorescer. Again, this language finds support in the very specification passage sanctioned previously by the Examiner.

There was also a prior art rejection leveled in the outstanding final Office Action; however, no response to Applicants' arguments was provided by the Examiner in the subsequent Advisory Actions. In discussions subsequent to issuance of the Advisory Actions, the Examiner indicated that no consideration had been given to Applicants' prior art arguments, since Applicants' allegedly ineffective addressing of the indefiniteness issues was thought to provide sufficient basis for maintaining the final rejection. Applicants therefore request that the Examiner now consider for the record their arguments against the prior art rejection. For the Examiner's convenience, these arguments are provided hereinbelow, taken verbatim from Applicants' May 2, 2002 response to the final Office Action.

The rejection of the claims under 35 USC §103(a) as being obvious over Elhammer in view of Mengin-Lecreulx et al. and Kohlrausch et al. has been maintained, again "for reason of record." The Examiner maintains that the Elhammer disclosure of the application of SPA in studying cellular processes combined with the alleged teachings of Mengin-Lecreulx and Kohlrausch with regard to peptidoglycan synthesis in *E. coli* would have led one of ordinary skill in the art to the instant invention. Again, Applicants emphatically disagree with the Examiner's assessment.

The Examiner states that "[A]bsent unexpected results, it would have been obvious to have applied" SPA "in detecting peptidoglycan synthesis." However, unexpected results are not the appropriate standard in the present context. The Examiner appears to believe that mere knowledge of the pathway of peptidoglycan synthesis, provided by the secondary references, would have enabled one of skill in the art to fill in the gaps in the teaching of the primary reference, and would somehow have countered some of the discouraging prior art teachings, thus motivating the skilled artisan to arrive at the instant invention. However, such knowledge provides no guidance for overcoming the obstacles well known in the art at that time, nor does it provide any encouragement to try to overcome said obstacles.

It must be emphasized that the Examiner's assessment of the "obviousness" of the instant invention could only have been arrived at by the use of impermissible hindsight. It must be appreciated that the enzymes used in the assay according to the instant invention are those involved in the final stages of peptidoglycan synthesis (classically referred to as stage 2 and 3 peptidoglycan synthesis where peptidoglycan is the final product) and represent so-called "downstream enzymes." As disclosed on page 3, lines 6-25 of the present application, methods for assaying the (downstream) enzymes have typically relied on paper chromatography, and this is confirmed, for example, in the Mengin-Lecreulx reference (see the experimental section on page 4628, left-hand column.) However, a drawback of using paper chromatography is that it is difficult to control the reaction conditions and, furthermore, it is entirely unsuitable for high throughput screening of compounds.

That the assay of downstream enzymes is recognized in the art to be difficult is illustrated, for example, in a passage from the first paragraph of the article of Men, et al., J. Am. Chem. Soc. **1998**, *120*, 2484-2485 (copy enclosed), published only a few months before the earliest claimed priority date of the present application:

> Although remarkable progress has been made in characterizing some of the early enzymes in

> the biosynthetic pathway, the downstream enzymes have proven exceedingly difficult to study. This is partly because the downstream enzymes are membrane-associated, making them intrinsically hard to handle, and partly because substrates for many of the enzymes are not readily available. These problems have impeded the development of active assays suitable for detailed mechanistic investigations of the downstream enzymes.

Bearing in mind that scintillation proximity assay (SPA) technology has been known from U.S. Patent No. 4,568,649 since 1986 (see page 6, lines 4 and 5 of Elhammer), the Examiner's contention that the assay according to the present invention is obvious is simply not credible. If such were the case, it would indeed be very surprising that it was not disclosed before, particularly since there has arguably been a long-felt need in the art for a straightforward and convenient method for assaying the downstream enzymes of the peptidoglycan biosynthetic pathway, particularly a method that can be used with membrane-bound enzymes (as demonstrated in the example of the present application) and also one that can be adapted for high throughput screening of compounds.

Notwithstanding that the presently claimed invention is nonobvious in view of the above arguments, Applicants present the following additional arguments in support of nonobviousness.

In arguendo, even if the prior art could be considered to provide a suggestion of the presently claimed invention (which

it cannot), at the very most this could only possibly be considered to make it obvious to try to obtain the present invention, rather than making the present invention obvious to do.

It is well-established that the standard of nonobviousness under 35 U.S.C §103 is *not obvious to try, but obvious to do*. (See In re O'Farrell, 853 F.2d 894, 7USPQ2d 1673 (Fed. Cir. 1988).) As determined in O'Farrell, an invention that is obvious to try is nevertheless nonobvious when the prior art makes it obvious to explore a new technology or general approach, for example SPA, that seemed to be a promising field of experimentation, but where the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it. The courts have also rejected an "obvious to experiment" approach; selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. (See In re Dow Chem. Co. 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).)

In view of Applicants' arguments in the previous sections, the cited prior art does not make the presently claimed invention obvious to do. A further indication that the prior art fails to make the presently claimed invention obvious to do is that the subject matter of the primary reference, Elhammer, and that of the present invention are only remotely related.

Specifically, in contrast to the presently claimed invention, Elhammer does not relate at all to enzymes, such as bacterial GlcNAc-transferase, required for peptidoglycan synthesis. Furthermore, the peptidoglycan synthetic pathway is found only in bacterial (prokaryotic) systems. Elhammer, however, relates to the eukaryotic enzyme GalNAc-transferase, which catalyzes the transfer of N-acetylgalactosamine to serine and threonine residues of polypeptides to form glycosylated proteins. (See Elhammer, page 2, line 6 - page 3, line 8.)

Furthermore, Elhammer actually teaches away from the use of SPA when a membrane-bound enzyme is involved in the catalytic process or pathway for which an assay is desired. (See Elhammer, page 3, lines 9-15.) This makes embodiments of the present invention which utilize membrane-bound transferase *not even* obvious-to-try.

It must also be appreciated that Elhammer provides an assay for the activity of a single eukaryotic enzyme involved in a one-step process, the *O*-glycosylation of polypeptides. This enzyme is not part of the complex, multistep prokaryotic peptidoglycan synthesis pathway of the instant invention. Thus, Elhammer only teaches and provides motivation for a reductionist approach, focused on identifying inhibitors of the single enzyme. In contrast, the presently claimed invention employs a

multi-enzyme, system-based approach by which compounds which inhibit any single activity, or even multiple catalytic activities, of the subject part of the peptidoglycan synthesis pathway can be identified. The system-based approach of the present invention provides the following advantages not provided by or suggested by the prior art.

First, when, as for the case of the present invention, the goal is to obtain inhibitors of the production of a product formed by a synthetic pathway, it is far more efficient to simultaneously screen for inhibitors of multiple parts of the pathway rather than to screen for inhibitors of each enzymatic activity separately. There is no suggestion of this advantage whatsoever in any of the cited prior art references.

Second, by measuring the success of inhibition of production of the end product, where it is the production of the end-product that is important (in this case, necessary for growth and survival of bacterial pathogens), the assay of the present invention, in contrast to single-enzyme types of assays, assures that the effect of an inhibitor identified by the assay on an enzyme within the pathway segment is not countered by regulation of another enzyme, so that production of the end-product is unaffected.

Third, by employing an entire segment of the peptidoglycan synthetic pathway, the presently claimed assay provides for the

possibility of identifying indirect inhibitors of enzymes within the subject pathway segment, i.e., inhibitors that do not directly inhibit a subject enzyme but that interfere with, for example, the allosteric regulation of the enzyme by another enzyme or by the upstream or downstream product of another enzyme. These sorts of inhibitors are not identifiable by a single-enzyme type of assay.

In view alone of the *per se* advantages described above, which are in no way suggested by or appreciated in the cited prior art, the presently claimed invention is nonobvious.

For all of the reasons set forth above, the present invention is nonobvious over the cited prior art. In summary, the Examiner has read far more guidance into the prior art than is warranted, and this is borne out by the facts, for example, that 1) the assay described in the primary reference and that instantly claimed cannot be said to be that similar and 2) despite the guidance alleged by the Examiner, no one in the ten years prior to Applicants' filing of the application is on record as having thought of developing the assay claimed in the instant application. In light of the actual state of the prior art at the time of filing, which included disclosure actually teaching away from the instant invention, and in light of the advantages provided by the instant invention, said invention

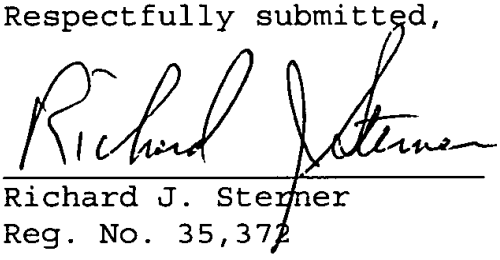
cannot be considered obvious in view of the cited prior art or in view of any other knowledge at the time.

In light of the amendments herein and the above arguments, the claims describe the invention with the definiteness required by statute, and the claimed subject matter is patentably distinct from the knowledge in the field at the time of filing. Reconsideration and allowance of pending claims 2-9 are respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Assistant Commissioner is hereby authorized to charge any fees which may be due for any reason to Deposit Account No. 23-1703.

Dated: December 9, 2002

Respectfully submitted,



Richard J. Sterner
Reg. No. 35,372

Applicants' Agent
Customer Number 007470

(212) 819-8200

Agent's Direct Line:
(212) 819-8783

VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (twice amended) An assay for detecting peptidoglycan synthesis, which comprises the steps of:

(1) incubating a reaction mixture comprising in aqueous medium a uridine(5'-)diphosphate (UDP)-*N*-acetylmuramylpentapeptide, radiolabelled UDP-*N*-acetyl glucosamine, a source of divalent metal ions, a source of undecaprenyl phosphate, a source of peptidoglycan, a source of translocase enzyme, a source of transferase enzyme, a[s] source of transglycosylase enzyme, a source of transpeptidase enzyme and a source of lipid pyrophosphorylase enzyme, under conditions suitable for peptidoglycan synthesis;

(2) adding a divalent metal ion chelator compound to the reaction mixture of step (1) to terminate peptidoglycan synthesis;

3) adding lectin-coated beads impregnated with a fluorescer to the reaction mixture of step (2), which beads bind, via the lectin coating, any radiolabelled peptidoglycan synthesized from the radiolabelled UDP-*N*-acetyl glucosamine precursor in step (1); and

(4) measuring light energy emitted by the fluorescer as a result of activation of the fluorescer by the radiation energy emitted by the proximately-bound, radiolabelled peptidoglycan, which

light energy is indicative of the presence of radiolabelled peptidoglycan synthesized in step (1).